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Ibogaine Perspectives of Psychotropic Drug Dependency Therapy

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Key words

Ibogaine – noribogaine – drug dependency – pharmacokinetics – pharmacodynamics – effects in animals and humans – toxicity

Introduction

Ibogaine, alkaloid of plant origin, is not yet an officially prescribed drug but experts consider it a perspective agent in drug dependency cure. The assumption is based on a couple of past open trials and virtually accidental uses of single doses of ibogaine or short-term ibogaine therapies resulting in long-term drug abstention for several months, or even years. The above-mentioned incredibly promising effect of ibogaine, as well as its sometimes questioned safety of application in pharmacotherapy, are currently begin tested in experimental and clinical trials. The results are interesting and so far encouraging. This article summarises current experience and new findings concerning ibogaine.

History and Present

Ibogaine is an alkaloid discovered in the roots of *Tabernanthe iboga* shrub (of *Apocynaceae* family, *Contonae* order) (see fig. 1) as well as in some other species growing in the rain forests of Central and Western Africa around the equator. The aborigines traditionally chewed the roots for treatment of fatigue, hunger and thirst. Higher doses, especially in extracts, changed the state of mind and were used for religious ritual purposes (best-know is the application in the “owiti” religion). Ritual effect of ibogaine was described in different ways. The aborigines believed that iboga roots procured their contact with their deceased ancestors and gods. In 19th century Europe first noticed stimulating and aphrodisiac effect of iboga root. The main active agent – the indole alkaloid called ibogaine – was first extracted from the root of iboga in 1901. Its exact structure, however, has only been known since 1957 (the first complete synthesis of ibogaine from nicotine-amide was performed in 1975) (for ibogaine structure see fig. 2). In early 20th century psychotherapists recommended ibogaine as a stimulating agent in treatment of and recovery from neurasthenia. In 1930s extracts containing ibogaine were sold under the names of Lambarene (France) or Iperton, as stimulating agents and muscle tonics without substantial establishment in medicinal practice. When in 1906s reports of hallucinogenic effects of ibogaine began to increase in number its application was prohibited in a number of

countries (including the U.S.A. in 1970).

A new revival of pharmaceutical interest in ibogaine was initiated by the incredible news of its effect in treatment of drug dependency. In 1962-1963 H. S. Lotsof (still in the United States) organised first open clinical sessions with heroin and cocaine dependent patients (the first one including himself). He reported that a single dose caused long-term disappearance of desire for the drug (craving) in some of the dependent patients, inhibiting abstinence symptoms in heroin-dependent patients. In about twenty years Lotsof returned to ibogaine (continuing his research in the Netherlands), trying to introduce it to the pharmaceutical market under the name of Endabus. Lotsof's ibogaine-based therapies were patented in stages (1985 – 1992) for treatment of opiate, cocaine, alcohol, nicotine and multiple dependency – U.S. patent, Lotsof – opiates (1985), cocaine (1986), alcohol (1989), nicotine (1991) and multiple dependency (1992). Application of ibogaine in controlled studies performed in the Netherlands was supported by NDA International from 1985. The results of the Dutch studies were very promising: Application of a single dose of ibogaine (20-25 mg/kg p.o.) led to six-month abstinence of minimum two thirds of the patients (out of the total number of 35 heroine and cocaine dependent), two-year or longer abstinence of 10% of the patients, and return to the drug after 14 days of only 10% of the patients. Lotsof also reported improved prognoses after repeated ibogaine sessions⁽¹⁾. Unfortunately, in the course of one of the studies a young heroine-dependent female patient died by an unlucky coincidence. The legal action against Lotsof discovered no neglect on the part of the therapist, and the applied dose of ibogaine was also low and usual (the ibogaine level in the blood of the deceased patient was 0.75 mg/l). It is maintained that the death might have been caused by simultaneous application of ibogaine and the drug (the patient probably secretly smoked heroin in the course of the session). This case, however, pointed out lack of scientific and pharmacological knowledge of ibogaine – mechanisms of its effect, pharmacokinetics etc. Another important conclusion drawn from the case was that ibogaine should in future be applied exclusively in hospitals where the patient is constantly supervised by specialists. Clinical studies in the Netherlands were discontinued and the focus of the research was moved to experimental preclinical level.

Preclinical studies confirmed effect of ibogaine in inhibition of symptoms of abstinence from opiates and inhibition of "autoapplication" of inhibiting and stimulating drugs, including alcohol and nicotine. A number of details increasing accuracy of pharmacokinetic and toxicological information were acquired (see below), including significant contribution of long-term effectiveness of the active metabolite of noribogaine to the effect of ibogaine. Other related metabolites and derivatives of ibogaine were tested, including 18-MK substance (18-metoxycoronaridine) with minimum toxicity even in high doses etc. Ibogaine was discovered to effect a number of neuromediating and other regulation systems.

At present clinical tests of ibogaine are continued, for example in cooperation with the Miami University, U.S.A. (Professor D. C. Mash) or the Panama University. Results of clinical study phase 1– safety

and kinetics – have been published, together with results of phase 2 of research – in first patients, and appear very perspective (see below). On the basis of current knowledge a preliminary conclusion can be drawn about safety of application of ibogaine and its active metabolite of noribogaine in drug dependent subjects, its inhibition of opiate abstinence symptoms after a single dose and inhibition of craving for heroine and cocaine after a single dose, with long-term effect in some patients, or extension of the effect by repeated sessions. Regarding the multiple effect of the substance on various neuromediators and potential effect on different types of dependencies (in animal experiments blocking autoapplication of opiates, amphetamine, cocaine, alcohol, nicotine) ibogaine may be considered beginning of a new trend in research into pharmacotherapy of drug dependence. Ibogaine and its derivatives might be applied in treatment of many more dependencies, including the frequent poly-drug dependencies so difficult to deal with. Of course further research will be necessary^(2,4).

Pharmacokinetics – Progress of Drug Through Human Body

Ibogaine is administered orally in capsules and easily absorbs into blood circulation. Doses of 10-20 mg/kg p.o. are considered effective in human drug dependency therapies. Ibogaine is relatively quickly metabolised in human as well as animal liver, with significant “first liver pass effect”. Ibogaine is metabolised mainly with the help of P450 cytochrome enzymes (CYP isoenzymes), especially CYP2D6 and CYP3A4. Most of the ibogaine volume is metabolised with CYP2D6 by O-demethylation resulting in production of an active metabolite – **noribogaine** (12-hydroxyibogamine). High blood levels of noribogaine are kept at the maximum for relatively long periods (exceeding 24 hours in men and women alike). Noribogaine is easily absorbed by the Central Nerve System (CNS) and regarding its below-mentioned pharmacological effects expected to produce much of the long-term anti-craving effect of ibogaine. The white population includes about 5-9% individuals with innate ineffectiveness of the CYP2D6 enzyme as a consequence of an autosomatic recessive genetic disposition related to that enzyme, which might manifest itself in certain differences in plasmatic levels and individually variable effect of ibogaine. Complex pharmacokinetic profiles of ibogaine and noribogaine in individuals receiving a single dose p.o. (500 mg in women and 800 mg in men) are already known. Ibogaine is lipophilic, therefore showing a strong trend towards stratification in the fat tissues of the body, where its levels are usually very high as late as 12 hours after administration, which supports the idea of partial depository effect of ibogaine. Experiments in rats further discovered differences in ibogaine and noribogaine distribution between sexes – systematic administration of the same dose of both substances resulting in three-times higher level of the substance in the brain of the females in comparison to males – and differences in certain pharmacological effects in both sexes were also demonstrated^(2,4).

Pharmakodynamics – Effect on Neuromediating Systems⁽²⁾

From the viewpoint of the presumed mechanisms of drug dependency the effect of ibogaine on the **dopamine system** is essential. Studies of binds showed no affinity of ibogaine whatsoever to dopamine D₁, D₂, D₃ and D₄ receptors. Very low doses (up to 1.5 mg/kg i.v.) significantly excite dopamine neurones in the ventral tegmental area (VTA) in rats. Regular doses of ibogaine, however, reduce (or leave intact) concentrations of dopamine (DA) in CNS, increasing concentrations of DA metabolites, including dihydroxyphenylacetic acid (DOPAC) and homovanillin acid (HVA), which demonstrates increased DA turnover shortly after ibogaine administration, possibly followed by long-term decrease of DA turnover. Similar effects are induced by **noribogaine** and **18-MK**. Kappa antagonists and naloxone antagonise this early effect of ibogaine (40 mg/kg, stratum). Participation of serotogenic receptors, and possibly of other systems, in regulation of DA release by ibogaine is assumed. The increased DA turnover after ibogaine administration may be caused by inhibition of vesicular DA transporters and consequently increased redistribution of DA from vesicles. The effect of drugs on DA transmission between mesolimbic neurons is affected by ibogaine as follows: a) As concerns drugs prevailingly acting on bodies of dopamine neurons (such as morphine, nicotine) ibogaine generally reduces the increased transmission of mesolimbic DA neurones caused by their application; b) as concerns drugs prevailingly acting on DA neuron terminals (such as cocaine or amphetamine) ibogaine shows different effects in different sexes – in female rats ibogaine initiates stimulation of DA neurons while inhibiting the same in male rats and mice.

Ibogaine binds to **opium** receptors, or shows higher affinity to kappa receptors and little or no affinity to mu and delta receptors. **Noribogaine** shows a much higher affinity to all three opium receptors than ibogaine (including 100 times higher affinity to kappa receptors). Ibogaine binds to **sigma receptors**, especially to sigma₂ (with low affinity to sigma₁ receptors). Noribogaine shows a much lower affinity to sigma₂ receptors and no affinity to sigma₁ receptors (18-MK does not bind to sigma receptors at all).

Ibogaine may affect **serotogenic** transmissions – increasing concentration of serotonin in nucleus accumbens, inhibiting serotogenic transporters and showing weak affinity to 5-HT_{1A}, 5-HT_{2A} and 5-HT₃ receptors. Ibogaine supports ability of serotogenic 5-HT₁ antagonists to stimulate DA release in stratum.

Ibogaine shows weak or no affinity to **cholinergic** muscarine receptors, blocking ganglionic (not neuromuscular) nicotine receptors, though. The bind is not fully reversible (potentially indicating long-term effect). Thus ibogaine long-term inhibits controlled release of catecholamine (adrenal chromaffinic cells) via nicotine receptors. Noribogaine has showed 20 times lower effectiveness in blocking responses controlled via the nicotine receptors.

Ibogaine is a non-competitive antagonist to NMDA **glutamate** receptors, with no affinity to kainite AMPA receptors or glutamate

receptors or metabotropic binds. Noribogaine shows about 5 times lower affinity to NMDA receptors.

Ibogaine non-competitively antagonises Ca^{2+} induced by contractions of aorta and mesenteric artery (by interference with the intracellular metabolism of calcium). Ibogaine shows no affinity to GABA-A receptors; with some affinity to **voltage-dependent sodium channels**. Ibogaine shows no affinity to cannabinoid receptors, reduces activities of NO-synthesis, induces weak hypoglycaemia in anaesthetic-treated rats, increases levels of corticosterones and prolactin.

Effects in animals⁽²⁾

Ibogaine (40 mg/kg i.p.) mildly inhibits **locomotory** of rodents depending on the dose and the sex of the subjects. **Noribogaine** (40 mg/kg i.p.) does not cause any inhibition. In general ibogaine (40 mg/kg i.p.) administered to female rodents supports locomotive stimulation induced by amphetamine and cocaine, showing an opposite effect on males (inhibiting induced hyperlocomotion). Ibogaine inhibits hyperlocomotion induced by morphine in males and females alike (more in females) including 5-10 mg/kg i.p. doses. (These different effects correlate with the effect on mesolimbic DA neurons – see below.) The inhibiting effect of ibogaine on morphine-induced hyperlocomotion can be antagonised by kappa and NMDA antagonists. Noribogaine (10-40 mg/kg i.p.) also inhibits morphine-induced hyperlocomotion in males and females, with low doses (10 mg/kg) supporting and higher doses inhibiting the effect in males.

Ibogaine (with its structure partly resembling harmaline) causes **shiver** in mice ($\text{ED}_{50} = 12 \text{ mg/kg s.c.}$ in mice) and in rats alike (depending on the dose, very mild as soon as at 10 mg/kg), with its effect weaker than that of harmaline. Unlike ibogaine, neither noribogaine nor 18-MK cause any shiver. Tremulous effect of ibogaine and relative substances is related to its effect on GABA routes.

Certain studies (“elevated plus maze” with two open and two closed wings) have demonstrated **moderate anxiety-generating** effect of ibogaine in rats (40 mg/kg i.p. after 22 hours) and in mice (2.5 mg/kg i.p.), with the lower dose of 1 mg/kg in mice causing anxiolytic effect. Similar anxious reactions shortly after administration of 10 mg/kg i.v. have been reported in cats and dogs too.

The most important properties of ibogaine tested for potential anti-craving effect include **inhibition of “autoapplication” of popular drugs**. Ibogaine (in doses between 10 – 40 mg/kg i.p.) inhibits autoapplication of **cocaine** in rodents (60-80%), like noribogaine and 18-MK. Depending on the dose (2.5-40 mg/kg i.p.) ibogaine inhibits autoapplication of **morphine** in rats, like noribogaine and 18-MK. Ibogaine (40 or 80 mg/kg i.p.) inhibits autoapplication of **heroin** in rats and the effect can be antagonised by kappa and NMDA antagonists. Ibogaine (10-80 mg/kg) also inhibits autoapplication of **alcohol** in alcohol preferring rats but only if administered i.p. or intragastrically and not when administered s.c., which supports the idea of participation of the metabolite in the effect generation. 18-MK also effectively inhibits autoapplication of alcohol.

Major effects of ibogaine in humans also include **inhibition of symptoms of abstention from opiates**. Experiments have proved this effect in rats and mice after both systemic and intracerebroventricular administration. The effect has also been confirmed in apes. A number of ibogaine derivatives have been tested, with ibogaine remaining the only preparation inhibiting opiate abstention symptoms. For example noribogaine has not shown this property at all. The NMDA antagonist component of the complex effect of ibogaine is assumed to contribute to the effect.

Ibogaine has never been active in **analgesic** tests where morphine and strong analgesics show effect – not even in the “tail-flick” test (up to 40 mg/kg i.p.), or in the “hot plate” test (up to 20 mg/kg i.p.). However, **effect has been demonstrated** in the course of **the peritoneal irritation test** (“phenylquinon writhing test”) with which weaker analgesics are tested (ED₅₀ of ibogaine was 9.7 mg/kg). Noribogaine (40 mg/kg) supported the effect of morphine in the “tail-flick” test in rats and mice (the effect lasting for maximum 19 hours). This effect of noribogaine is probably related to its high affinity to kappa and mu opiate receptors (Even though this reasoning seems insufficient, subsequent tests have indicated contribution of non-opiate contraceptive mechanisms to the overall effect of ibogaine).

In comparison to other psychoactive substances (psilocybine, bufotenine etc.) Ibogaine shows insignificant effect on **aggressiveness** of isolated mice and on evoked attacking behaviour of rats.

Repeated administration of ibogaine has **never developed dependency** in rats (based on the applicable scale of the primary physical dependency test) ibogaine has no **rewarding or aversive effects** as demonstrated by the conditioned preference or aversion to place test. Ibogaine (40 mg/kg) has only demonstrated reduction of preference to place created by morphine or amphetamine (this effect probably not related to effect on the opiate receptor system).

Ibogaine does not affect development of space **memory** (40 mg/kg). (The earlier reported falsely positive inhibiting effect was caused by inhibition of locomotory). On the contrary, ibogaine and **noribogaine** in low doses (0.25-2.5 mg/kg) facilitate retrieval of routes from memory.

Ibogaine increases **blood pressure** (BP) in vigilant dogs. This effect can be blocked by atropine. In sleeping dogs with administered anaesthetics ibogaine causes blood pressure drop and reduces heartbeat frequency drop. Therefore central stimulation effect of ibogaine can be assumed. Ibogaine also supports the effect of adrenaline on blood pressure. Ibogaine (50 mg/kg) reduced **heartbeat frequency** in dogs.

Effects on humans^(2,3,4)

A number of dose-dependent central **psychotropic effects** of ibogaine have been reported in humans. Effects of **extract from the root of *Tabernanthe iboga*** are more complex and can differ from the effects of ibogaine itself. The root extract in sufficient doses evokes fantastic visual images, feelings of excitement, drunkenness, mental

confusion to hallucination. The extract from iboga root is certainly a CNS stimulating agent, high doses being likely to cause spasms, paralysis and eventually breath stop. High doses may also cause hearing, visual and taste synaesthesia and moods ranging from deep sorrow to rejoicing euphoria. Oral application of ibogaine or root extract may generate subjective effects lasting for about 6 hours. About 50% of ibogaine treated individual described confusion, gesture dis-coordination, nausea, vomiting. Typical symptoms include sleepiness, with the subject unwilling to move, open its eyes, communicate (even though being able to communicate). Many subjects react with increased sensitivity to light and preference for darkness. Noise and sounds are very irritating. The resulting condition resembles sleep, although the person is conscious. The subjects have described fantastic images in quick succession, like a quickly projected film or quickly changing slides. The contents of the images have differed, often including typical archetypal contents, personal experience, problems, past decisions and relationships, including images of animals and other people. Although the fantasies can be manipulated by both the subject and the psychotherapist, the quick succession of images is easy to break. That is why the activity of psychotherapist focuses on the period immediately following the session itself. Higher doses of ibogaine may cause visual and other hallucinations, often combined with fear and evil apprehensions.

Preliminary results of **clinical trials phase 2** (39 patients, application of a single dose, 1 month follow up) have so far demonstrated effect of ibogaine in the course of detoxification of opiate-dependent patients and in short-term stabilisation of drug-dependent subjects before or in early stages of therapy. Ibogaine has significantly reduced craving for cocaine and heroine during detoxification. Depressive symptoms in patients (self-assessment) have also been reduced, the improvement as a rule being preserved until the end of the therapeutic programme (30 days).

Toxicity

LD50 of ibogaine has been determined in guinea pigs (82 mg/kg i.p.) and in rats (327 mg/kg intragastric, 145 mg/kg i.p.) Chronic administration of ibogaine in rats – 10 mg/kg i.p. for 30 days or 40 mg/kg i.p. for 12 days – did not result in any **pathological effect** on liver, kidneys or brain. No pathologic effects have been demonstrated in apes taking ibogaine in doses of 5-25 mg/kg p.o. for four subsequent days⁽²⁾.

Certain earlier references note **neurotoxic** degenerative change in Purkyně cells in little brain in rats after administration of ibogaine in the dose of 100 mg/kg i.p., including astrocytoma and microgliosis. The above-mentioned neurotoxicity is not likely to be related to NMDA effect of ibogaine. Some of the above-described changes are sometimes related to ibogaine effect on sigma₂ receptors. The neurotoxic effects have not manifested themselves in mice and in rats have been limited to high doses. The “typical” dose of 40 mg/kg causes significant effect to neither male nor female rats. The same

lack of toxicity has been demonstrated by repeated doses of 10 mg/kg, including apes. Acute effect of **18-MK** (100 mg/kg) does not cause any pathological effect on little brain. The described indications of neurotoxicity of ibogaine are related to administration of relatively high doses of ibogaine, never used in therapy. Ibogaine may also demonstrate **neuroprotective** effects (for example preventing lethal effect of NMDA in mice and minimising occurrence of spasms after electrical shock in mice)⁽²⁾.

Results of **clinical trials phase 1** have already been published – for safety and kinetics⁽⁴⁾. Subjects (n=40) receiving 500, 600 or 800 mg p.o. have not shown any significant adverse reactions, the most frequent adverse reactions including nausea and mild shiver or mild transient ataxia within 1 hour after administration. Vital sign checks (breath frequency, systolic and diastolic blood pressure and pulse) have not shown any significant change within 24 hours after administration for study or therapeutic purposes. The lymphocyte (neutropic) counts, the levels of sodium and potassium were within the limits. No significant changes have been observed in ALT, AST, alkaline phosphatase (ALP) and GGT. Intense monitoring has discovered no haemodynamic or electrocardiographic changes. Just two heavily crack dependent patients showed hypotension at the beginning of the session. No acute or post-study adverse psychiatric effects, nor any brain dysfunctions have been reported. It can therefore be concluded that ibogaine administered in an isolated dose has been well tolerated by subjects and no significant risks reducing its safety have been observed.

Conclusion

It can be concluded that to-date research has supported suitability of ibogaine application, including some of its derivatives, in drug dependency therapies. In preclinical experiments ibogaine has reduced autoapplication of cocaine, morphine, heroine, nicotine and alcohol, weakened opiate abstinence symptoms, blocked conditioned place preference induced by morphine and amphetamine. No trend towards development of dependency or toleration of ibogaine has been observed. Ibogaine interacts with a number of neuromediating systems of CNS, many of them related to mechanisms of development of desire for drugs – craving (for example ibogaine non-competitively blocks NMDA receptors, interacts with dopamine transporters and kappa opiate receptors). Reduction of opiate abstinence syndromes is ascribed to NMDA receptor blocking. Anti-craving effect of ibogaine is probably complex and implemented with participation of multiple mechanisms and various neuromediating systems, including effect on the traditional dopamine route. The idea of a very long-term effect of ibogaine in drug dependent subjects, with a single dose or a short-term therapy sufficient for months or years of abstinence, will still need more verification. Short-term effect in the detoxification stage in humans has already been proved. Ibogaine inhibits abstinence symptoms after opiates and significantly reduces craving for heroine and cocaine. It is clear that ibogaine is not of the substitution therapy

drug type. Long-term effective contribution of an active metabolite – noribogaine – to the overall long-term effect of ibogaine is assumed but further research is still needed. The warning reports of toxicity and neurotoxicity of ibogaine have been tested with the conclusion that the adverse effects are related exclusively to high doses not used in therapy. Stage 1 clinical study has demonstrated that ibogaine in effective doses of 10-20 mg/kg p.o. is safe, well tolerated by patients and generating no significant adverse effects (with the exception of nausea and mild shiver at the beginning of the therapeutic period). Ibogaine and/or some of its derivatives therefore represent a promising trend in research into new medicines for drug dependency therapy, currently in progress on the clinical study level.

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